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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,505	12/10/2001	Peter W. Laird	47675-9	8355

22504 7590 06/30/2005

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/016,505	LAIRD ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-36,38-47,49-59 and 61-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-36,38-47,49-59 and 61-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed April 28, 2004. Currently, claims 27-36, 38-47, 49-59, 61-68 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action is FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 27-34, 36, 38-45, 47, 49-57, 59, 61-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000) in view of Wittwer et al (US Pat. 6,140,054, October 2000).

Herman et al. (herein referred to as Herman) teaches a method of detection of methylated nucleic acids using agents which modify unmethlated cytosine and distinguishing modified methylated and non-methylated nucleic acids. Herman teaches a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite, amplifying the converted nucleic acid with primers which distinguish between unmethylated and methylated nucleic acids such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Herman teaches using MSP primers that are specifically designed to recognize CpG sites to take advantage of the differences in methylation to amplify specific products to be identified (col. 5, lines 3-5). Herman teaches that the "only technique that can provide more direct analysis than MSP for most CpG sites within a defined region is genomic sequencing" (col. 5, lines 30-35). Herman teaches a method for detecting a methylated CpG containing nucleic acid by obtaining nucleic acid and treating the nucleic acid with an agent that modifies unmethylated cytosine (col. 5, lines 58-63). The agent is preferably sodium bisulfite which modifies unmethylated cytosine, but not methylated cytosine (col. 6, lines 9-13)(limitations of Claim 29-30). Moreover, amplification is carried out using primers specific for CpG-specific oligonucleotides such

that the primer distinguish between modified methylated and non-methylated nucleic acids and finally detecting the methylated nucleic acids (col. 5, lines 60-67). Herman teaches that treatment with sodium bisulfite modifies unmethylated cytosine. This allows the allele specific detection of methylated nucleotides. Herman teaches that the amplified products are preferably identified as methylated or non-methylated by sequencing (col. 9, lines 51-55). Among the sequencing methods suggested by Herman, allele-specific oligonucleotide probe analysis is listed (col. 9, lines 55-65). Allele-specific oligonucleotide (ASO) probes are specific probes which allow differentiation between different sequences. ASO probe detection is among the list of means for sequencing the amplified products to identify methylated or non-methylated sequences.

Herman does not specifically teach using a FRET probe to detect allele specific differences in genomic DNA which have been treated with bisulfite to analyze methylation status of the nucleic acid.

However, Wittwer et al. (herein referred to as Wittwer) teaches a method of using FRET probes to detect polymorphisms. Wittwer teaches that the methods of ASO hybridization require time consuming multiple manual steps. Therefore, Wittwer uses melting temperatures of fluorescent hybridization probes that hybridize to a PCR amplified region to identify polymorphisms (col. 1, lines 30-35). Wittwer teaches that in a preferred embodiment the hybridization probe comprises two oligonucleotide probes that hybridize to adjacent regions of a DNA sequence wherein each oligonucleotide probe is labeled with a respective member of a FRET pair (col. 2, lines 45-50). The

presence of the target nucleic acid sequence in a biological sample is detected by measuring fluorescent energy transfer between the two labeled oligonucleotides (col. 2, lines 45-50). Wittwer teaches in combination with standard melting curve analysis, single point mutations in a gene can be distinguished from the normal gene (col. 3, lines 20-25). Wittwer also teaches that one of the labeled oligonucleotides also functions as a PCR primer ("probe-primer"), then the two fluorescently labeled oligonucleotides hybridize to opposite strands of a DNA sequence (col. 3, lines 40-45)(limitations of Claim 36). Wittwer teaches designing oligonucleotide probes identical in sequence to the complementary wild type sequence which will dissociate from the locus containing a mutation at a lower temperature than it will from the wild type locus (col. 4, lines 5-15). The probes of Wittwer contain fluorescent labeled dyes that when in close proximity the resonance energy transfer is high (col. 9, lines 7-10). The probes may comprise multiple sets of FRET oligonucleotide pairs which can be labeled with different fluorescent resonance energy transfer pairs (col. 12, lines 55-65). The method allows for a rapid procedure that can be conducted within a single reaction vessel for detecting polymorphisms in genomic DNA samples (col. 7, lines 15-25). Specifically Wittwer teaches that the method comprises the steps of combining a biological sample comprising nucleic acid sequences with a pair of oligonucleotide PCR primers and two or more FRET oligonucleotide pairs, adding a thermostable polymerase, amplifying a selected segment of the nucleic acid sequence by the polymerase chain reaction and illuminating the biological sample and monitoring the fluorescence as a function of temperature (col. 7, lines 20-30).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the method of Herman which detected allele specific differences in genomic DNA following bisulfite treatment using ASO probes with the allele specific detection method of Wittwer. Herman specifically teaches treating the nucleic acid with bisulfite prior to amplification and detection. Since the genomic nucleic acid has been treated to convert un-methylated nucleic acids, the sequence differs between the methylated and unmethyalted nucleic acids. Herman teaches that ASO probes are a means of sequencing to determine whether the nucleic acid is identified as methylated or non-methylated (col. 9, lines 50-60). The ordinary artisan would have recognized based upon the teachings of Wittwer that ASO hybridization require time consuming multiple manual steps and would have been motivated to have modified the method to encompass a more efficient method of detection. Wittwer specifically teaches the method of using FRET probes to detect the presence of alleles or polymorphisms is less time consuming and require less manual steps. Moreover, Wittwer's method allows detection in a single reaction vessel. Therefore, the ordinary artisan would have been motivated to have detected allele specific differences in bisulfite treated DNA using FRET probes for the specific benefits taught by Wittwer.

With respect to Claim 38-45, 47, 49, the claims specifically require that the primer do not distinguish between modified and unmethylated and methylated nucleic acids. Herman specifically states that amplified products may be identified as methylated or non-methylated by sequencing such as by allele-specific oligonucleotides. Thus, it

would follow that any amplified product whether or not the nucleic acid was first amplified with primers which distinguished between modified unmethylated and methylated nucleic acids would allow detection by allele specific oligonucleotides. Without using primers that are methylation specific would provide greater versatility to the assay and would allow obtaining an amplicon which was either methylated or unmethylated. Given the teachings in Herman that nucleic acids may be identified as methylated or non-methylated by sequencing, the ordinary artisan would have been motivated to have detected methylation status within these sequences by FRET probes which were taught in the art to be preferable to ASO probes taught in Herman. The ordinary artisan would have been motivated to have detected the allele differences using FRET probes during amplification for the reasons specifically articulated in Wittwer.

Response to Arguments

The response explains the instant invention and the method of Herman. The response asserts that Herman does not disclose or suggest CpG-specific oligonucleotide probes. This argument has been reviewed but is not convincing because following bisulfite treatment, the nucleotide sequence within a CpG island is differentially altered between methylated regions and non-methylated regions. Herman specifically teaches that the amplified products may be identified as methylated or non-methylated by sequencing such as ASO probes. ASO probes may detect the differences C and T in methylated vs unmethylated nucleic acids. The instant specification and the prior art provides detail regarding how bisulfite treatment alters a

polynucleotide. Specifically, bisulfite treatment of DNA converts all unmethylated cytosines to uracil. Herman specifically teaches that the conversion of an unmethylated cytosine to another nucleotide which will distinguish the unmethylated from the methylated cytosine is a modification. The uracil is recognized as a thymine by Taq polymerase and therefore upon PCR, the resultant product contains cytosine only at the polisiton where 5-methylcytosine occurs in the starting template (col. 6, lines 5-22). Once the nucleic acid is treated with bisulfite or another modifying agent, the polynucleotides differ in sequence analogous to different alleles. The methylated cytosines remain cytosines and the unmethyalted cytosines are converted to thymidine. Hence, differences between methylated and unmethylated sequences are reduced to differences in sequence. Differences in sequence may be detected using sequencing, allele, specific oligonucleotides, oligomer restriction, ligation assays, for example (as taught by Herman, col. 9, lines 50-60). Further the prior art is full of methods for detecting differences in sequences.

The response argues that the method of Whittwer is only a quasi real-time method. This argument has been thoroughly reviewed, but is not found persuasive because the instant claims are drawn to detecting, contemporaneously with amplification the methylated nucleic acid based on at least one of amplification-mediated probe displacement and amplification-mediated change of probe fluorescence. The method of Whittwer states that the continuous monitoring of fluorescence during the PCR reactions provides a system for detecting sequence alterations internal to the PCR primers by resonance energy transfer and probe melting

curves (col. 16, lines 5-10). With respect to "real-time amplification", Whittwer specifically teaches that Figure 17 and 18 are directed to real-time amplification. Whittwer teaches that real time monitoring of a rapid cycling PCR reaction can be conducted through the use of fluorescent dyes and fluorescently labeled probes (col. 7, lines 42-45). Moreover, Whittwer teaches the method of conducting a PCR amplification reaction while simultaneously determining the fluorescence change as a function of temperature allows for a more rapid genotyping of the target loci. Previously only endpoint detection was possible because of instrument limitations, however several instruments have been provided. Whittwer thus teaches performing continuous monitoring of fluorescence during the PCR reaction to provide a system for detecting sequence alterations internal to the PCR primers by resonance energy transfer and probe melting curves (col. 16, lines 5-10). The teachings of Whittwer are directed to real-time continuous monitoring of fluorescence during or contemporaneously with PCR amplification as required by step c of Claim 27, for example.

The response asserts that the instant method does not require determination of melting curves as the claimed methods of Whittwer. This argument has been thoroughly reviewed, but is not found persuasive because the claims do not particularly exclude such a limitation. The instant claims are openly and broadly drawn to a method of detecting, during the amplification the methylated nucleic acid based on at least one of amplification-mediated probe displacement and amplification-mediated change of probe fluorescence.

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claims 27-35, 38-46, 49-58, 61-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herman et al (US Pat. 6,017,704, January 25, 2000) in view of Whitcombe et al (US Pat. 6,270,967, August 2001).

Herman et al. (herein referred to as Herman) teaches a method of detection of methylated nucleic acids using agents which modify unmethlated cytosine and distinguishing modified methylated and non-methylated nucleic acids. Herman teaches a method for detecting cytosine methylation and methylated CpG islands within genomic sample of DNA by contacting the sample of genomic DNA with bisulfite, amplifying the converted nucleic acid with primers which distinguish between unmethyalted and methylated nucleic acids such that at least one oligonucleotide probe is a CpG specific probe and detecting the methylated nucleic acid based on an amplification mediated change or property thereof in relation to another probe or primer. Specifically Herman teaches using MSP primers that are specifically designed to recognize CpG sites to take advantage of the differences in methylation to amplify specific products to be identified (col. 5, lines 3-5). Herman teaches that the "only technique that can provide more direct analysis than MSP for most CpG sites within a defined region is genomic sequencing" (col. 5, lines 30-35). Herman teaches a method for detecting a methylated CpG containing nucleic acid by obtaining nucleic acid and treating the nucleic acid with an agent that modifies unmethylated cytosine (col. 5, lines

58-63). The agent is preferably sodium bisulfite which modifies unmethylated cytosine, but not methylated cytosine (col. 6, lines 9-13)(limitations of Claim 29-30). Moreover, amplification is carried out using primers specific for CpG-specific oligonucleotides such that the primer distinguish between modified methylated and non-methylated nucleic acids and finally detecting the methylated nucleic acids (col. 5, lines 60-67). Herman teaches that the amplified products are preferably identified as methylated or non-methylated by sequencing (col. 9, lines 51-55). Among the sequencing methods suggested by Herman, allele-specific oligonucleotide probe analysis is listed (col. 9, lines 55-65). Allele-specific oligonucleotide (ASO) probes are specific probes which allow differentiation between different sequences.

Herman does not specifically teach using a TaqMan probe to detect allele specific differences in genomic DNA which have been treated with bisulfite to analyze methylation status of the nucleic acid.

However, Whitcombe illustrates the use of a TaqMan probe (xyz) for allele discrimination of the ASO element (Figure 10, col. 8, lines 58-62). Whitcombe teaches that when using TaqMan for allele discrimination the ASO element of the approach requires that the probe annealing is borderline to obtain maximum differentiation between the variants. Whitcombe teaches that the use of TaqMan probe allows realtime or end point detection of the released fluorophore. As seen in Figure 11, Whitcombe teaches a method of using molecular beacons which make use of a similar quenching effect (col. 8, lines 65-68).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified an improved the method of Herman which detected allele specific differences in genomic DNA following bisulfite treatment using ASO probes with the allele specific detection method for detection of allele specific detection using a TaqMan probe as suggested by Whitcombe. Herman specifically teaches treating the nucleic acid with bisulfite prior to amplification and detection. Since the genomic nucleic acid has been treated to convert un-methylated nucleic acids, the sequence differs between the methylated and unmethyalted nucleic acids. Herman teaches that ASO probes are a means of sequencing to determine whether the nucleic acid is identified as methylated or non-methylated (col. 9, lines 50-60). Whitcombe specifically teaches using a TaqMan probe in the ASO detection of an allele. Therefore, the ordinary artisan would have recognized that using a TaqMan probe as opposed to an ASO hybridization would have the expected benefits of realtime detection of the released fluorophore. Therefore, the ordinary artisan would have been motivated to have detected allele specific differences in bisulfite treated DNA using FRET probes for the specific benefits taught by Whitcombe.

With respect to Claim 38-46, 49, the claims specifically require that the primer do not distinguish between modified and unmethylated and methylated nucleic acids. Herman specifically states that amplified products may be identified as methylated or non-methylated by sequencing such as by allele-specific oligonucleotides. Thus, it would follow that any amplified product whether or not the nucleic acid was first amplified with primers which distinguished between modified unmethylated and

methylated nucleic acids would allow detection by allele specific oligonucleotides. Without using primers that are methylation specific would provide greater versatility to the assay and would allow obtaining an amplicon which was either methylated or unmethylated. Given the teachings in Herman that nucleic acids may be identified as methylated or non-methylated by sequencing, the ordinary artisan would have been motivated to have detected methylation status within these sequences by FRET probes which were taught in the art to be preferable to ASO probes taught in Herman. The ordinary artisan would have been motivated to have detected the allele differences using Taqman or beacon probes during amplification for the reasons specifically articulated in Whitcombe.

Response to Arguments

The response explains the instant invention and the method of Herman. The response asserts that Herman does not disclose or suggest CpG-specific oligonucleotide probes. This argument has been reviewed but is not convincing because following bisulfite treatment, the nucleotide sequence within a CpG island is differentially altered between methylated regions and non-methylated regions. Herman specifically teaches that the amplified products may be identified as methylated or non-methylated by sequencing such as ASO probes. ASO probes may detect the differences C and T in methylated vs unmethylated nucleic acids. The instant specification and the prior art provides detail regarding how bisulfite treatment alters a polynucleotide. Specifically, bisulfite treatment of DNA converts all unmethylated cytosines to uracil. Herman specifically teaches that the conversion of an unmethylated

cytosine to another nucleotide which will distinguish the unmethylated from the methylated cytosine is a modification. The uracil is recognized as a thymine by Taq polymerase and therefore upon PCR, the resultant product contains cytosine only at the polisiton where 5-methylcytosine occurs in the starting template (col. 6, lines 5-22). Once the nucleic acid is treated with bisulfite or another modifying agent, the polynucleotides differ in sequence analogous to different alleles. The methylated cytosines remain cytosines and the unmethyalted cytosines are converted to thymidine. Hence, differences between methylated and unmethylated sequences are reduced to differences in sequence. Differences in sequence may be detected using sequencing, allele, specific oligonucleotides, oligomer restriction, ligation assays, for example (as taught by Herman, col. 9, lines 50-60). Further the prior art is full of methods for detecting differences in sequences.

The response asserts that there is no suggestion in the art to combine a real-time allele discrimination method with a methylation assay that is dependent on methylation detection. This argument has been thoroughly reviewed, but is not found persuasive because Whitcombe and the art teach the benefits of performing a real-time assay. Real-time assays provide a continuous idea of the assay and its changes throughout PCR. Whitcombe specifically teaches that "when using the TaqMan for allele discrimination the ASO element of the approach requires that the probe annealing is borderline to obtain maximum differentiation between the two variants. The new system is more easily optimisable because of the probe and drive elements are user-selected

and can be optimized once for all amplicons" (col. 8, lines 57-63). Thus, Whitcombe directs the ordinary artisan how to use the TaqMan probe for ASO analysis.

In response to applicant's argument based upon the age of the references, contentions that the references are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

Thus for the reasons above and those already of record, the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 27-32, 38-43, 50-55, 61-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-26 of U.S. Patent No. 6,331,393 (December 18, 2001).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably

distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claim 27-32, 38-43, 50-55, 61-67 of the instant application is generic to all that is recited in Claim 1-26 of U.S. Patent No. 6,331,393. That is, Claim 1-26 of 6,331,393 falls entirely within the scope of Claim 27-32, 38-43, 50-55, 61-67, or in other words, Claim 27-32, 38-43, 50-55, 61-67 is anticipated by Claim 1-26 of 6,331,393. Here, claim 27 recites a method for detecting cytosine methyaltion and methylated CpG islands by contacting a genomic sample of DNA with a modifying agent, amplifying the nucleic acid with primers and detecting the methylated nucleic acid based on an amplification- medicated, or amplification product-mediated change in a property of the CpG-specific probe or in a property thereof in relation to another probe or primer. The claims of U.S. Patent No. 6,331,393 are directed specifically to detecting the methylated nucleic acid based on amplification-mediated displacement of the Cp-G specific probe. Therefore, the specific detection means claimed falls within the scope of the broad genus of detection methods allowed in Claim 27, 38, 50. Moreover, the Claims drawn to the kits, namely Claim 61 of the instant application and Claim 20 of 6,331,393 differ only in the recitation of the probe which is based on amplification-mediated displacement. Therefore, the claims are not patentable distinct from one another.

Response to Arguments

The response indicates that Applicants are fully prepared to timely file a Terminal Disclaimer upon notification of allowable subject matter. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

9. No claims allowable.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
June 27, 2005

Jasemine C. Chambers

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